Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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Boris Schmidt & Greta R. Patzke

To cite this article: Boris Schmidt & Greta R. Patzke (1999) Fmoc-N-allyl Glycine Derived N-allyl-2,5-Diketopiperazines, Synthetic Communications, 29:6, 1025-1032, DOI: 10.1080/00397919908086067

To link to this article: http://dx.doi.org/10.1080/00397919908086067

Published online: 17 Sep 2007.

SYNTHETIC COMMUNICATIONS, 29(6), 1025-1032 (1999)

FMOC-N-ALLYL GLYCINE DERIVED N-ALLYL-2,5-DIKETOPIPERAZINES

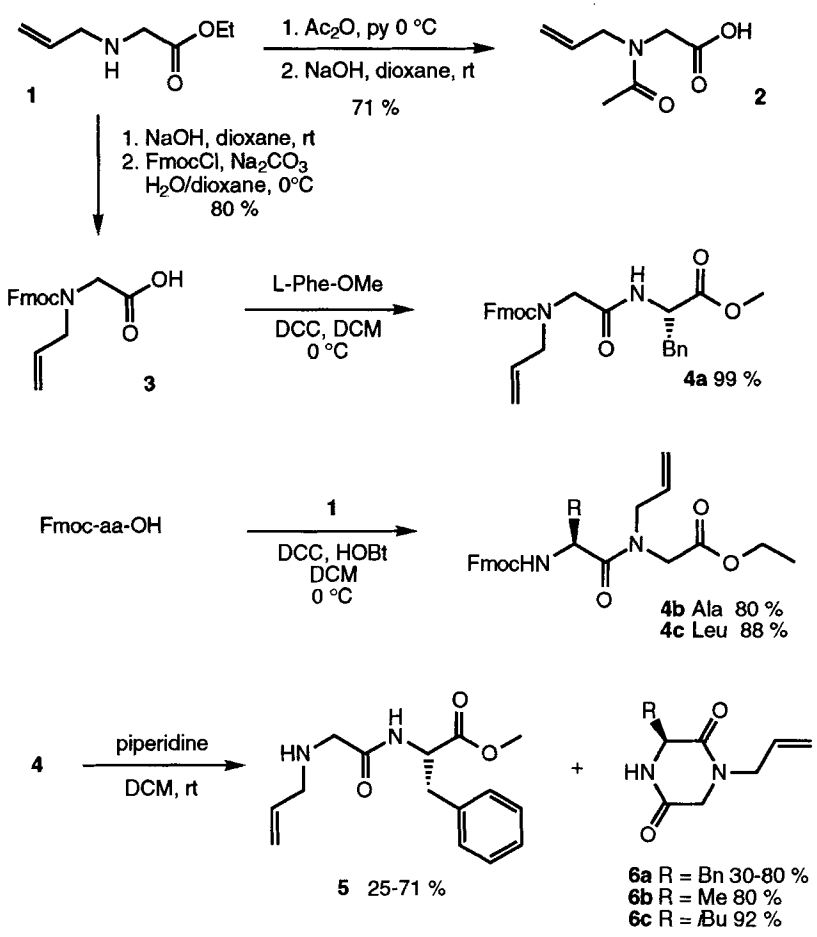
Boris Schmidt,* Greta R. Patzke

Institut für Organische Chemie der Universität Hannover, Schneiderberg 1b, D-30167 Hannover, Germany, Fax: (49)-511-762 3011, boris.schmidt@mbox.oci.uni-hannover.de

Abstract: The title compound was prepared from chloroacetic acid and elongated to dipeptides, which cyclized spontaneously upon Fmoc-deprotection to form N-allylated 2,5-diketopiperazines.

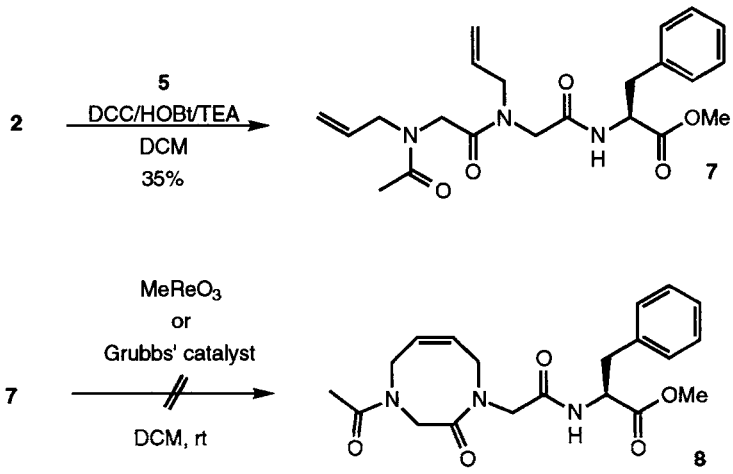
A new approach to constrained peptides was pioneered by R. Grubbs, who used ring closing metathesis (RCM) of 1,4-bis-*C*-allylated peptides[1-4] to synthesize β-turn analogues. This stimulated us to design a similar approach to angiotensin II peptide mimetics, yet with 1,3-bis-allylated peptides. The Grubbs method had limitations in the prize and availability of enantiomerically pure *C*-allyl amino acids. Recently this was overcome by Kazmeier's[5,6] enantioselective rearrangement of glycine allylester enolates and commercial (*S*)-*N*-Fmoc-allylglycine.[7] We still decided to use *N*-allylated glycine,[8] because it promises additional conformational freedom over *C*-allylated glycine due to enhanced cis/trans isomerisation of amide bonds and avoids the problems arising from insufficient enantiopurity. We developed a set of capping and elongation reagents for the homogeneous synthesis of *N*-allylated peptides such as the *N*-acetyl-*N*-allyl glycine **2** and *N*-Fmoc-*N*-allyl glycine **3**, starting from easily available[8] *N*-allylglycine ester **1**.

*To whom correspondence should be addressed.



An acetylation, followed by base hydrolysis provided the crystalline acid **2** in 71 % yield. The Fmoc-protected *N*-allylglycine can be accessed from **1** by hydrolysis, followed by treatment with Fmoc-chloride or at inferior yield from *N*-allylglycine hydrochloride[9] and Fmoc-succinimide (42 %). DCC mediated condensation provided the 3 dipeptides **4a-c** at 80 - 99 % yield. The deprotection by piperidine under controlled conditions gave dipeptides such as **5**. Higher temperatures or extended reaction times led to exclusive formation of the corresponding 2,5-diketopiperazines **6a-c**. Such 2,5-diketopiperazines are

frequently encountered as antibiotic and antitumoral[10] degradation products of peptides and proteins[11,12] or as scaffolds in combinatorial chemistry.[13] Their formation is common for peptoids[14] (*N*-alkylated peptides) yet the observed reaction rates and yields are unusual. The attempted purification of 1- or 2-*N*-allylated dipeptides actually increased the yield of diketopiperazines, irrespective of the allyl positioning (**4a** and **4b,c**) and the carboxy termini. The extended reaction time favours the intramolecular cyclisation. However, a solid phase supported synthesis with rapid deprotection, followed by fast coupling of the remaining amino acids, avoids this obstacle.[15]



The facile diketopiperazine formation forced us to adopt a new strategy towards the desired 1,3-bis-*N*-allylated peptides, because just one 2,3-bis-*N*-allylated peptide **7** was accessible by the initial route. This peptide did not cyclize to the new turn structure **8** by RCM utilizing methyltrioxorhenium[16-18] or $(PCy_3)_2Ru(CHPh)Cl_2$. This failure may be attributed to chelation of a 6-membered cyclic intermediate, as it was postulated by Fürstner et al.,[19] which traps the ruthenium and slows down the reaction, or to the considerable strain of the targeted 11-membered ring. The formation of such 11-membered rings by RCM

has not been reported yet.[20] Most likely, the build up of transannular interactions favours polymerisation over cyclisation.

EXPERIMENTAL SECTION

Chemistry. General Comments. Melting points (uncorrected): open glass capillaries, Büchi apparatus – ^{1}H and ^{13}C NMR spectra: Bruker WP 200, Bruker AM 400, at 200 (50.3) MHz and 400 (100.58) MHz. Chemical shifts are reported as δ values (ppm) downfield from Me_4Si. – IR spectra: Perkin Elmer 1710 FT and 1600 FT and Bruker IFS 25, recorded in $\nu_{max.}(cm^{-1})$. Mass spectroscopy: Finnigan MAT 312, VG Autospec (FAB, HRMS). Elemental analysis: Elementar Vario EL. Column chromatography: Merck and Baker silica gel 60 (40-63 μm and 15-40 μm), Et_2O (ethyl ether), EE (ethyl acetate) PE (light petroleum, bp 40-60 °C). TLC was carried out using aluminium sheets precoated with silica gel 60 F_{254} (0.2 mm, E. Merck). Chromatographic spots were visualised by UV and/or spraying with an acidic, ethanolic solution of *p*-anisaldehyde, or an ethanolic solution of ninhydrin, followed by heating. DCM, DMSO, $CHCl_3$ and DMF were distilled and stored over 3 Å molecular sieves. Organic phases were dried over $MgSO_4$.

***N*-Acetyl-*N*-allylglycine (2)** *N*-Allylglycine[8] (715 mg, 5.0 mmol) was treated with acetic anhydride (0.65 ml, 6.88 mmol) in pyridine (5 mL) for 3 h at 0 °C. The solvent was removed *in vacuo* prior to treatment with NaOH (0.6 g, 15 mmol) in dioxane/water (15 mL, 10:1). The solvent was evaporated and the residue was treated by 2 N HCl until the pH reached 3. The aqueous phase was extracted by EE (3x 40 mL). The dried and concentrated extracts were crystallised from $CHCl_3$/PE 1:2 to give colorless prisms (560 mg, 71 %), m.p. 73 °C. $C_7H_{11}N$, fw: 157.17. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) 2.17 (s, 3H), 4.00 (d, ^{3}J = 2.8, 2H, 1'), 4.12 (s, $2H_\alpha$), 5.12-5.30 (m, 2H), 5.68-5.86 (m, 1H, 2'). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS) 20.77, 47.16, 55.21, 117.8, 131.8, 171.7, 172.48

(CON); IR ($CHCl_3$) ν = 3000bs, 1742vs, 1648vs, 1472m, 1420m. MS (70 eV): *m/z* (%) 157 (7, M^+), 114 (100), HRMS: calc. 157.0738861, found 15.073685. CHN-analysis: calc. C 53.49, H 7.05, N 8.91, found C 53.44, H 6.98, N 8.86.

N-(9-Fluorenylmethoxycarbonyl)-N-allylglycine (**3**) *N*-Allylglycine*HCl[9] (455 mg, 3.00 mmol) was dissolved in 0.9 N Na_2CO_3 solution (8 mL) and dioxane (4.5 mL). The solution was cooled to 0 °C and treated with Fmoc-succinimide (1.012 g, 3.00 mmol) over 2 h. After 24 h 100 mL of water were added and extracted by Et_2O (2x 35 mL). The aq. phase was adjusted to pH 3 by conc. HCl and extracted by EE (3x 100 ml). The dried extracts were concentrated to give Fmoc-N-AllGly as a colorless oil (810 mg, 80 %), $C_{20}H_{19}NO_4$, fw.: 337.38. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) 3.85 (s, 1H), 3.97 (m, 2H; 1'), 4.04 (s, 1H), 4.24 (dt, ^3J = 6.9, 1H), 4.46 (d, ^3J = 6.9, 2H; OCH_2), 5.14 (m, 2H, 3'), 5.72 (m, 1H), 7.1-7.8 (m, 8H). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS) 31.74, 47.2, 50.75, 76.17, 117.75, 118.3, 119.97, 124.84, 127.79, 132.84, 141,33, 144.29, 155.92, 156.51. IR ($CHCl_3$) ν = 1728s, 1700vs, 1236s, 1120s. MS (70 eV): *m/z* (%): 337 (1, M^+), 297 (1), 178 (100). CHN-analysis: calc. H 5.68 C 71.2 N 4.15, found H 5.59 C 71.0, N 4.02.

***N*-Fmoc-*N*-allylglycylphenylalanine methylester** (**4a**) 1-Hydroxy-1H-benzotriazene (74 mg, 0.54 mmol), *N,N'*-dicyclohexylcarbodiimide (114 mg, 0.55 mmol) and **3** (169 mg, 0.50 mmol) were stirred and suspended at 0 °C in dry methylene chloride (2 mL) under nitrogen. After 30 min at 0 °C, PheOMe*HCl (108 mg, 0.50 mmol) was added and the pH was adjusted to 7.5 (diisopropylethylamine). The reaction mixture was stirred for 18 h at ambient temperature under nitrogen and then filtered. Concentration and purification by column chromatography (silica gel, ethyl acetate) afforded **4a** (247 mg, 99 %) as a colorless oil. $C_{30}H_{30}N_2O_5$, fw: 498.58. ^1H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS) 1.83 (dm, 2H; CH_2Ph), 3.06 (m, 2H; $C\underline{H}_2CHCH_2$), 3.20 (m, 1H; $H_{\alpha Phe}$), 3.65 (s, 3H; OCH_3), 3.79 (s, 2H; $H_{\alpha Gly}$), 3.87 (s, 1H; NH), 4.13 - 4.22 (m, 1H; $CH_2C\underline{H}CH_2$), 4.40 - 4.49 (m, 2H,

$CH_2CHC\underline{H}_2$), 7.00 - 7.80 (m, 13H). IR ($CHCl_3$) ν = 2932m, 1740s, 1688s, 1516m, 1244s; MS (70 eV): *m/z* (%): 461 (3) , 449 (2), 178 (100). CHN-analysis: calc. C 72.27, H 6.06, N 5.62, found C 71.92, H 6.21, N 5.86.

***N*-Allylglycyl-phenylalanine methylester (5) 4a** (166 mg, 0.31 mmol) was dissolved in dry methylene chloride (2 mL) under nitrogen at ambient temperature. Dry piperidine (167 mL, 2.32 mmol) was added *via* syringe and the mixture was stirred for 55 min. Concentration and purification by column chromatography (silica gel, EE) afforded **5** (60 mg, 71 %) as a colorless oil. $C_{15}H_{20}N_2O_3$, fw: 276.34. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS) 1.55 (s, 1H), 2.95 - 3.25 (m, 6H), 3.65 (s, 3H; OCH_3), 4.80 (m, 1H; $H_{\alpha Phe}$), 4.90 - 5.15 (m, 1H; $CH_2C\underline{H}CH_2$), 5.60 - 5.80 (m, 2H; CH_2), 6.95 - 7.30 (m, $5H_{arom}$), 7.55 (s, 1H; NH); IR ($CHCl_3$): ν = 3000 m, 1744s, 1672s, 1516m, 1236w; MS (70 eV): *m/z* (%): 276 (40), 244 (11). The compound reacts at room temperature to the diketopiperazine, therefore no elemental analysis was obtained.

(*S*)-1-Benzyl-3-allyl-2,5-diketopiperazine (6a). **6a** formed during prolonged deprotection of **4a** with dry piperidine (3-20 h). Column chromatography (silica gel, EE) provided **6a** (30 %-80 %) as colorless plates. $C_{14}H_{16}N_2O_2$, fw: 244.2 ^{1}H-NMR (400 MHz, CD_3OD, 25 °C, TMS) 3.02 (m, 2H), 3.11 (ddd, ^{3}J = 4.4, 2H; CH_2Ph), 3.71 - 3.96 (m, 2H; 1'), 4.31 (dd, ^{3}J = 4.4, 1H; C1-C$\underline{H}$), 5.08 - 5.18 (m, 2H; 3'), 5.53 - 5.65 (m, 1H; 2'), 7.12 - 7.32 (m, 5 H_{arom}); IR ($CHCl_3$) ν = 3392w, 3008m, 1664vs, 1452m, 1224s; MS (70 eV): *m/z* (%): 244 (39), 230 (4), 204 (56), 154 (47), 91 (100). CHN-analysis: calc. C 68.83, H 6.6, N 11.47, found C 66.99, H 6.56, N 11.30.

(*S*)-1-Methyl-3-allyl-2,5-diketopiperazine (6b). Dry piperidine (1 mL, 10.1 mmol) was added to a solution of **4b** (838 mg, 1.92 mmol) in dry DCM (10 mL) at ambient temperature. After stirring for 20 h, the solvent was evaporated off at

room temperature and purification by gradient filtration (silica gel, $CHCl_3$-PE, 1:3) provided **6b** (257 mg, 80 %) as a colorless oil. $C_8H_{12}O_2N_2$, fw: 168.197. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS) 1.51 (d, ^3J = 6.5, 3H; Me), 3.92 (s, $2H_{\alpha Gly}$), 4.02 - 4.03 (m, 2H; 1'), 4.11 (q, ^3J = 6.5, $1H_{\alpha Ala}$), 5.20 - 5.31 (m, 2H; 3'), 5.68 - 5.80 (m, 1H; 2'); ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C, TMS) 19.95, 48.66, 49.07, 50.99 (1'), 119.32 (3'), 131.03 (2'), 166.42, 166.67; IR ($CHCl_3$): ν = 3396w, 3008m, 1688vs, 1668s, 1448m, 1316m; MS (70 eV): *m/z* (%): 167 (16), 152 (5), 126 (11). CHN-analysis: calc. C 57.13 H 7.19 N 16.66, found C 55.45, H 6.94, N 16.00.

***N*-Acetyl-*N*-allylglycyl-*N*-allylglycylphenylalanine methylester (7)**

1-Hydroxy-1H-benzotriazene (32 mg, 0.24 mmol), *N,N'*-dicyclohexylcarbodiimide (50 mg, 0.24 mmol) and *N*-acyl-*N*-allylglycine (35 mg, 0.22 mmol) were dissolved in dry DCM (2 mL) under nitrogen. After 30 min at 0 °C, **5** (60 mg, 0.21 mmol) in dry methylene chloride (1 ml) was added *via* syringe. The mixture was stirred under nitrogen at 0 °C for 2 h and then allowed to reach ambient temperature over 18 h. The precipitate was filtered off and the residue was rinsed with cold DCM. The collected organic extracts were concentrated under reduced pressure and purified by LC (silica gel, $CHCl_3$-EE, 40:1) to afford **7** (32 mg, 35 %) as a colorless oil. $C_{22}H_{29}N_3O_5$, fw: 415.49. ^{1}H-NMR (400 MHz, CD_3OD, 25 °C, TMS) 2.12 (s, 3H; CH_3), 2.88 - 3.15 (m, 1H), 3.13 - 3.25 (m, 1H), 3.67 - 3.73 (d, 3H; OCH_3), 3.80 - 4.18 (m, 8H), 4.25 (d, 2H), 4.67 - 4.78 (m, $1H_\alpha$), 5.05 - 5.25 (m, 4H; 2H, 3'), 5.60 - 5.93 (m, 1H; 2'), 7.17 - 7.33 (m, 5 H_{arom}); IR ($CHCl_3$): ν = 3000m, 2936m, 1744s, 1664vs, 1436m, 1248m; MS (70 eV): *m/z* (%): 415 (9, M^+), 400 (2), 372 (25), 356 (2), 329 (2).

Acknowledgement. Financial support by the Deutsche Forschungsgemeinschaft, DAAD/SI and the Studienstiftung des deutschen Volkes (G.R.P.) is gratefully acknowledged

REFERENCES AND NOTES

(1) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855.

(2) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606.

(3) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

(4) Hafner, A.; van der Scharf, P. A.; Mühlebach, A. *Chimia* **1996**, *50*, 131.

(5) Kazmaier, U.; Krebs, A. *Angew. Chem.* **1995**, *107*, 2213.

(6) Kazmaier, U. *Liebigs Ann. Chem.* **1997**, 285.

(7) (*S*)-*N*-Fmoc-allylglycine is commercially available by ChiroTech.

(8) Speziale, A. J.; Jaworski, E. G. *J. Org. Chem.* **1960**, *25*, 729.

(9) Marletta, M. A.; Kenyon, G. L. *J. Biol. Chem.* **1979**, *254*, 1879.

(10) Arison, B. H.; Beck, J. L.; Maeji, N. J.; Valerio, R. M.; Campbell, R. A. *Tetrahedron* **1973**, *29*, 2743.

(11) Bray, A. M.; Geysen, H. M. *J. Org. Chem.* **1991**, *48*, 6659.

(12) Steinberg, S. M.; Bada, J. L. *J. Org. Chem.* **1983**, *48*, 2295.

(13) Szardenings, A. K.; Harris, D.; Lam, S.; Shi, L.; Tien, D.; Wang, Y.; Patel, D. V.; Navre, M.; Campbell, D. A. *J. Med. Chem.* **1998**, *41*, 2194; Szardenings, A. K.; Burkoth T. S.; Lu H. H.; Tien D. W., Campbell, D. A. *Tetrahedron* **1997**, *53*, 6573.

(14) Humphrey, J. M.; Chamberlain, A. R. *Chem. Rev.* **1997**, *97*, 2243.

(15) Schmidt, B.; Kühn, C.; Ehlert, D. K.; Patzke, G. R.; Lindeberg, G.; Lindman, S.; Karlén, A.; Hallberg, A. *Chem. Eur. J.* **1998**, submitted.

(16) Schmidt, B. *J. Prakt. Chem.* **1997**, *339*, 493.

(17) Herrmann, W. A.; Wagner, W.; Flessner, U. N.; Volkhardt, U.; Komber, H. *Angew. Chem.* **1991**, *103*, 1704.

(18) Schneider, M. F.; Junga, H.; Blechert, S. *Tetrahedron* **1995**, *51*, 13003.

(19) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

(20) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. I* **1998**, 371.

Accepted 8-8-98